SUPPLEMENTARY INFORMATION

A Convenient In-Flow Preparation of Cr(II) Chloride for Nozaki-Hiyama-Kishi Reaction

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1. General Experimental:

Continuous-flow reactions were performed on reactor X-Cube™ (ThalesNano Inc., Hungary) at atmospheric pressure. Melting points were determined on a Stuart SMP 30 Melting Point Apparatus and are not corrected. NMR spectra (δ , ppm; J , Hz) were measured on Bruker Avance-400 instrument in CDCl₃ and referenced to the solvent signal. Data are reported in the following order: chemical shifts; multiplicities - indicated br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent). UPLC-MS analyses were performed on Acquity UPLC Instrument (Waters Corporation), GC on Agilent GC-MS System (GC 7890A, inert MSD 5975C, Agilent Technologies). Qualitative and quantitative XRF analyses were performed on X-ray fluorescence spectrometer SPECTRO iQ II. THF was purchased from Penta, distilled under atmospheric pressure and dried over 4 Å molecular sieves (water content below 10 ppm; measured by Karl Fischer Coulometer Mettler Toledo DL 32). All used chemicals were obtained from Sigma-Aldrich or AlfaAesar and used without further purification.

2. Preparation of Chromium Dichloride

2.1 Generation of the reagent

Al_2O_3 (neutral, particle size 0.05-0.15 mm, Brockmann activity I) and CrCl_3 (sublimed) were grinded with mortar and pestle until homogeneous (cca 1 min), sieved (particle size 0.05 to 0.4 mm), mixed with the reduction metal and packed into the cartridges (flow reactor X-Cube®). After activation at the given temperature for 10 min, the flow was set on and the eluate (3 mL) collected. The content of Cr(II) was determined iodometrically (For optimization, see Table S1).

2.2 Titration experiments

A part of the eluate (0.3 mL) was diluted with water to the volume 5 mL and titrated with standardized 0.01-M iodine solution. After slight over-titration, the excess of iodine was determined by precise titration with $\text{Na}_2\text{S}_2\text{O}_3$ with the starch indicator.

2.3 Blind and leaching experiments

Blind experiment: When during the cartridge filling the CrCl_3 or zinc was omitted, no product of the Nozaki-Hiyama-Kishi reaction was formed and only the starting material was detected.

Leaching experiments: The content of metal in the eluate was tested by X-ray fluorescence spectroscopy.

Detailed procedure: a) Chromium leaching: Al_2O_3 (1.25 g) and CrCl_3 (sublimed, 0.25 g) were grinded with mortar and pestle until homogeneous (cca 1 min), sieved (particle size 0.05 to 0.4 mm) and packed into the cartridges. After activation at 100 °C for 10 min, the flow 0.2 mL/min was set on and the eluate (3 mL) collected and analyzed. The content of Cr was found to be only in traces (under the detection limit, see Fig. S1, red line). b) Zinc leaching: Al_2O_3 (1.25 g) and zinc (0.5 g) were mixed and packed into the cartridges. After activation at 100 °C for 10 min, the flow 0.2 mL/min was set on and the eluate (3 mL) collected and analyzed. The content of Zn was found to be only in traces (under the detection limit, see Fig. S1, blue line). c) Chromium and Zn leaching: Al_2O_3 (1.25 g) and CrCl_3 (sublimed, 0.25 g) were grinded with mortar and pestle until homogeneous (cca 1 min), sieved (particle size 0.05 to 0.4 mm), mixed with zinc (0.5 g) and packed into the cartridges. After activation at 100 °C for 10 min, the flow 0.2 mL/min was set on and the eluate (3+3 mL) collected and analyzed (Fig. S2).

Fig. S1. X-ray fluorescence spectrum of the eluate of the leaching experiments a,b.
Blue line: Zn leaching, red line: Cr leaching.

Fig. S2. X-ray fluorescence spectrum of the eluate of the leaching experiment c.
Blue line: 1st portion of the eluate, red line: 2nd portion of the eluate.

Table S1. Optimization of the Cr(III)-Cr(II) reduction in-flow^a

	Al ₂ O ₃ (g)	CrCl ₃ (g)	Red. metal (g)	Activ.temp. (°C)	Flow (mL/min)	Cr(II) yield (%)
1	1.750	0.079	Zn, 0.300	85	0.2	22.0
2	1.500	0.158	Zn, 0.300	100	0.3	25.0
3	1.250	0.181	Zn, 0.600	100	0.3	21.8
4	1.250	0.250	Zn, 0.500	100	0.2	32.1
5	1.000	0.316	Zn, 0.600	85	0.2	28.5
6	0	0.052	Zn ^b , 2.960	100	0.2	12.0
7	1.250	0.079	Mn ^c , 0.110	100	0.2	16.0
8	0.600	0.158	Mn ^c , 1.850	150	0.1	24.0
9	0.500	0.079	Mn ^c , 3.600	100	0.1	- ^d
10	0	0.316	Mn ^c , 4.800	100	0.2	40.0 ^e

^aFor two cartridges (approx. vol. 1.6 mL, cartridges were filled up to 90% of their volume);

^bGranular, particle size 0.2 mm; ^cPowder, particles 325 mesh; ^dHigh pressure, system blocked;

^eMn re-used after regeneration from the cartridge, yield of Cr(II) 20%.

3. Nozaki-Hiyama-Kishi reaction¹

Scheme 1. NHC reaction. Substituents R, R' are given in Table S2.

Typical experiment:

The solution of halogen derivative (0.15 mmol), aldehyde (0.2 mmol) and NiCl₂ (1 mg) in 1 mL DMA:THF 10:1 was degassed and treated with the eluate (2.7 mL) obtained as given above, row 4, Table S1. Progress of the reaction was monitored with GC-MS or UPLC-MS. After stirring at 50 °C for the time given in Table S2, the green reaction mixture was diluted with water (20 mL) and allowed to crystallize at RT (compounds **2a-2g**), or extracted with ether (3x50 mL), organic layer washed with brine (6x20 mL) and dried with MgSO₄. The crystalline material resulting after evaporation was recrystallized from ethanol (compounds **1a, 1b**). The isolated yields and CrCl₂ amounts are given in Table S2.

Table S2. Yields of NHK reaction

	R'	R	<i>n</i> (CrCl ₂) (mmol)	Time (h)	Product	Isolated yield (%)
1	H	C ₆ H ₅	0.40	21	1a	80.3
2	H	4-CH ₃ -C ₆ H ₄	0.42	24	1b	90.4
3	4-CH ₃	C ₆ H ₅	0.43	20	1b	89.8
4	2-CO ₂ CH ₃	C ₆ H ₅	0.39	16	2a	86.2
5	2-CO ₂ CH ₃	4-CH ₃ -C ₆ H ₄	0.41	16	2b	80.4
6	2-CO ₂ CH ₃	4-CH ₃ O-C ₆ H ₄	0.42	5	2c	92.4
7	2-CO ₂ CH ₃	2-Cl-C ₆ H ₄	0.43	2	2d	88.3
8	2-CO ₂ CH ₃	4-CO ₂ CH ₃ -C ₆ H ₄	0.39	4	2e	65.2
9	2-CO ₂ CH ₃	3-Br-C ₆ H ₄	0.43	2	2f	94.3
10	2-CO ₂ CH ₃	C ₁₁ H ₂₃	0.40	16	2g	76.7

4. Characterization of the prepared compounds

1a

Diphenylmethanol (**1a**)

The title compound was made from iodobenzene (30.6 mg) and benzaldehyde (21.2 mg).

White solid, 22.2 mg, m.p. 68.1-68.5 °C (ref.² 68.0-68.5 °C). Elem. anal.: For C₁₃H₁₂O (184.24) calc. (%): C, 84.75; H, 6.57; O, 8.68; found (%): C, 84.75; H, 6.53. ¹H NMR (ref.³) (400 MHz, CDCl₃) δ 7.40-7.32 (m, 8H), 7.27 (m, 2H), 5.85 (s, 1H), 2.24 (brs, 1H). ¹³C NMR (ref.³) (101 MHz, CDCl₃) δ 144.13, 128.84, 127.92, 126.88, 76.60.

Phenyl(*p*-tolyl)methanol (**1b**)

The title compound was made from iodobenzene (30.6 mg) and *p*-tolualdehyde (24.0 mg), or from 4-iodotoluene (32.7 mg) and benzaldehyde (24.0 mg), resp. White solid, 26.9 mg and 26.7 mg, resp., m.p. 53.2-54.2 °C (ref.⁴ 54.5-55.0 °C). Elem. anal.: For C₁₄H₁₄O (198.27) calc. (%): C, 84.81; H, 7.12; O, 8.07; found (%): C, 84.79; H, 7.08. ¹H NMR (ref.⁵) (400 MHz, CDCl₃) δ 7.41-7.37 (m, 2H), 7.31-7.36 (m, 2H), 7.26 (d, *J* = 13.6 Hz, 2H), 7.25 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.82 (s, 1H), 2.34 (s, 3H), 2.19 (brs, 1H). ¹³C NMR (ref.⁵) (101 MHz, CDCl₃) δ 144.28, 141.29, 137.63, 129.52, 128.79, 127.79, 126.86, 126.78, 76.44, 21.45.

3-Phenylisobenzofuran-1(3*H*)-one (**2a**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and benzaldehyde (21.2 mg). White solid, 28.3 mg, m.p. 116.0-116.4 °C (ref.⁶ 115-117°C). Elem. anal.: For C₁₄H₁₀O₂ (210.23) calc. (%): C, 79.98; H, 4.79; O, 15.22; found (%): C, 79.63; H, 4.74. ¹H NMR (ref.⁷) (400 MHz, CDCl₃) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.39 m (1H), 7.37 (d, *J* = 5.7 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.28 (dd, *J* = 6.7, 2.9 Hz, 2H), 6.41 (s, 1H). ¹³C NMR (ref.⁷) (101 MHz, CDCl₃) δ 170.86, 150.02, 136.75, 134.65, 129.70, 129.65, 129.32, 127.32, 126.02, 125.96, 123.19, 83.07.

3-(*p*-Tolyl)isobenzofuran-1(3*H*)-one (**2b**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and *p*-tolualdehyde (24.0 mg). White solid, 27.0 mg, m.p. 130.2-131.1 °C (ref.⁸ 127 °C). Elem. anal.: For C₁₅H₁₂O₂ (224.26) calc. (%): C, 80.34; H, 5.39; O, 14.27; found (%): C, 80.13; H, 5.34. ¹H NMR (ref.⁷) (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.22 – 7.10 (m, 4H), 6.38 (s, 1H), 2.35 (s, 3H). ¹³C NMR (ref.⁷) (101 MHz, CDCl₃) δ 170.91, 150.16, 139.68, 134.59, 133.74, 129.98, 129.62, 127.40, 126.09, 125.95, 123.21, 83.11, 21.58.

3-(4-Methoxyphenyl)isobenzofuran-1(3*H*)-one (**2c**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and anisaldehyde (27.2 mg). White solid, 33.3 mg, m.p. 114.6-115.1 °C (ref.⁸ 114 °C). Elem. anal.: For C₁₅H₁₂O₃ (240.26) calc. (%): C, 74.99; H, 5.03; O, 19.98; found (%): C, 74.98; H, 5.15. ¹H NMR (ref.⁷) (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 8.00 – 7.90 (m, 1H), 6.37 (s, 1H), 3.80 (s, 3H). ¹³C NMR (ref.⁷) (101 MHz, CDCl₃) δ 170.85, 160.76, 150.10, 134.57, 129.64, 129.14, 128.64, 126.29, 125.92, 123.27, 114.67, 83.07, 55.69.

3-(2-Chlorophenyl)isobenzofuran-1(3*H*)-one (**2d**)

The title compound⁹ was made from methyl 2-iodobenzoate (39.3 mg) and 2-chlorobenzaldehyde (28.2 mg). White solid, 32.4 mg, m.p. 111.4-111.8 °C (ref.⁹ 108-110 °C). Elem. anal.: For C₁₄H₉ClO₂ (244.67) calc. (%): C, 68.73; H, 3.71; Cl, 14.49; O, 13.08; found (%): C, 68.33; H, 3.63. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.5 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 9.4 Hz, 1H), 6.95 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.84, 149.80, 134.83, 133.15, 130.53, 130.40, 130.28, 129.87, 127.86, 127.80, 126.16, 125.69, 123.26, 79.38.

Methyl 4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)benzoate (**2e**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and methyl 4-formylbenzoate (32.8 mg). White solid, 26.2 mg, m.p. 131.2-131.7 °C. HR-MS: For C₁₆H₁₂O₄Na calc. 291.06278, found 291.06289. ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.5, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 6.9 Hz, 1H), 6.45 (s, 1H), 3.92 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.84, 166.76, 149.47, 141.65, 134.86, 131.35, 130.63, 129.99, 127.01, 126.26, 125.67, 123.03, 82.17, 52.61.

3-(3-Bromophenyl)isobenzofuran-1(3*H*)-one (**2f**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and 3-bromobenzaldehyde (37.0 mg). White solid, 40.9 mg, m.p. 148.1-148.6 °C. Elem. anal.: For C₁₄H₉BrO₂ (289.13) calc. (%): C, 58.16; H, 3.14; Br, 27.64; O, 11.07; found (%): C, 58.44; H, 3.15. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.1 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.43 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.22 (m, 3H), 6.35 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.48, 149.37, 139.04, 134.88, 132.77, 130.92, 130.22, 130.01, 126.23, 125.86, 125.76, 123.38, 123.11, 81.96, 77.36.

3-Undecylisobenzofuran-1(3*H*)-one (**2g**)

The title compound was made from methyl 2-iodobenzoate (39.3 mg) and dodecanal (36.9 mg). White solid, 33.2 mg, m.p. 45.3-48.1 °C. HR-MS: For C₁₉H₂₈O₂Na calc. 311.19815, found 311.19816. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 5.53 - 5.41 (m, 1H), 2.42 - 2.30 (m, 2H), 2.10-1.95 (m, 2H), 1.75 - 1.70 (m, 2H), 1.60-1.55 (m, 2H), 1.50 - 1.45 (m, 2H), 1.40 - 1.25 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.04, 150.49, 134.24, 129.35, 126.52, 126.06, 122.04, 81.81, 35.12, 34.12, 32.25, 29.94, 29.86, 29.74, 29.68, 25.17, 25.04, 23.03, 14.47.

5. NMR spectra of the prepared compounds

6. References

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